Treosulfan and gemcitabine in metastatic uveal melanoma patients: results of a multicenter feasibility study

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No effective treatment currently exists for metastatic uveal melanoma. However, recent results obtained by an ATP-based tumor chemosensitivity assay have shown consistent activity of treosulfan + gemcitabine in up to 80% of tumor specimens tested. In this study we describe the first clinical results observed with this drug combination at different European centers in patients with metastatic uveal melanoma. Clinical case series of patients with metastatic uveal melanoma were treated with treosulfan + gemcitabine at seven different centers. Fourteen patients, 13 previously untreated and one pretreated with chemoimmunotherapy, were included in the study. Patients received treosulfan + gemcitabine in four different dose regimens. The response rates, progression-free and overall survival, and toxicity were evaluated. The analysis of 14 patients revealed one complete response, three partial responses and a stable disease in eight cases. The objective response rate was 28.6%, the median overall survival was 61 weeks [95% confidence interval (CI) 54–133 weeks], the progression-free survival was 28.5 weeks (95% CI 13–62 weeks) and the 1-year survival rate was 80%. The drugs were well tolerated. The most common side-effects were leuko- and thrombocytopenia. These preliminary results suggest potential therapeutic benefit of treosulfan + gemcitabine treatment in metastatic uveal melanoma and warrant further controlled studies. *Anti-Cancer Drugs* 14:337–340 © 2003 Lippincott Williams & Wilkins.

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Introduction

Uveal melanoma is the most common primary malignancy of the eye with an annual incidence of approximately six to seven cases per million [1]. In contrast to cutaneous melanoma, it often and preferentially metastasizes to the liver [2]. Systemic therapy is usually unsuccessful and the median survival time of patients with liver metastases is only 5–7 months [3]. Uveal melanoma cells are highly resistant to cytotoxic drugs and chemotherapy is usually unsuccessful [3,4]. Intra-arterial chemotherapy with fotemustine and cisplatin in part combined with chemoembolization or surgical resection of liver metastases was reported to be effective at least in a small number of patients [5–8]. The administration of bleomycin, vincristine, lomustine, dacarbazine (BOLD) and interferon (IFN)-α revealed an objective response of 20%, but was associated with severe pulmonary toxicity in 15% of the patients [9]. An EORTC multicenter trial using this regimen was stopped prematurely due to pulmonary toxicity. Therefore, there is no standard treatment for patients with metastatic uveal melanoma. Recent *ex vivo* studies using an ATP-based tumor chemosensitivity assay (ATP-TCA) demonstrated consistent activity of the drug combination of treosulfan + gemcitabine against primary choroideal melanoma cells [10,11]. This *ex vivo* observation was confirmed by Neale *et al.*, showing that 80% of 77 choroidal melanomas were sensitive to this drug combination [12]. Neuber *et al.* treated 14 stage IV cutaneous melanoma patients with treosulfan as second-line therapy, and observed one complete remission, two partial remissions and three patients with stable disease [13].

Based on these preliminary results, we have analyzed the multicenter experience with pilot studies using treosulfan + gemcitabine in metastatic uveal melanoma patients. Due to the rareness of this tumor type, the performance of a regular phase I/II trial was impossible. Therefore, four different chemotherapy regimens were used in this feasibility study based on dose schemes formerly used in the treatment of breast and ovarian cancer, and which seemed to be workable in metastatic uveal melanoma.

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Material and methods

Patient characteristics

Fourteen patients (six males and eight females) with metastatic uveal melanoma were included in the study. The median age of the population was 63 years. Thirteen patients were treated with treosulfan + gemcitabine as first-line therapy, one patient showed progressive disease after two cycles of a chemoimmunotherapy with dacarbazine, BCNU, cisplatin, tamoxifen, IFN-α and interleuklin-2, and was treated with treosulfan + gemcitabine as second-line therapy.

Eligibility criteria

Patients had to meet the following eligibility criteria: metastatic uveal melanoma with bidimensionally measurable metastases; age ≥ 18 years; an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; no severe medical or psychiatric illness; and adequate bone marrow, hepatic and renal function. From January 1998 to December 2001 all patients with metastatic uveal melanoma in the six participating European centers were asked to attend in this clinical study. A written informed consent was obtained from all patients enrolled in this trial.

Response assessment

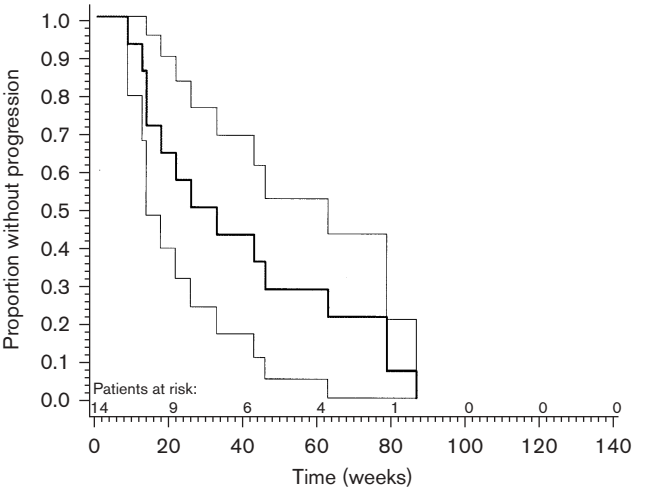
Prior to therapy, patients were evaluated by physical examination, including ECOG performance status, routine laboratory tests including blood cell counts and serum chemistry, and computed tomography (CT) scans to assess measurable disease. During chemotherapy treatment, laboratory tests were done every 7 days. CT scans of measurable disease were repeated after every 2 cycles. Toxicities were recorded and graded using WHO toxicity criteria [14]. Tumor responses were graded using standard criteria: a complete remission required the disappearance of all measurable disease, signs, symptoms and biochemical changes related to the tumor for ≥ 28 days, during which time no new lesions could appear. A partial response required reduction of $\geq 50\%$ in the sum of the products of the greatest perpendicular dimensions of all measurable lesions lasting for ≥ 28 days, during which time no new lesions could appear. Progressive disease was defined as an increase of $> 25\%$ in the sum of the products of the greatest perpendicular dimensions of all measurable lesions or the development of any new lesions. Progression-free survival was measured from entry into the treatment protocol until the first documented progression. Patient survival was analyzed by Kaplan–Meier methodology (Fig. 1).

Treatment regimen

Patients received combined chemotherapy with treosulfan and gemcitabine in four different regimens (1: treosulfan 5 g/m^2 and gemcitabine 1 g/m^2 on day 1 every 21 days; 2: treosulfan 5 g/m^2 and gemcitabine 1 g/m^2 on day 1 every 28 days; 3: treosulfan 5 g/m^2 and gemcitabine 0.5 g/m^2 on day 1 every 21 days; 4: treosulfan 3.5 g/m^2 and gemcitabine 1 g/m^2 on day 1 and 8 every 21 days). All patients received ondansetrone 8 mg orally or i.v. 1 h prior to treatment.

The doses of treosulfan or gemcitabine were reduced by 25% for grade III hematologic toxicity. Any grade IV toxicity prompted discontinuation of protocol therapy.

Fig. 1



Time of progression-free survival (weeks). The thick line represents the mean value of all patients, thin lines represent the 95% CI.

Results

Administration of chemotherapy

In total, 92 cycles of chemotherapy with treosulfan + gemcitabine in four different regimens were administered during the study. Three cycles were given according to regimen 1, 22 cycles were given according to regimen 2, 33 cycles were given according to regimen 3 and 16 cycles were given by regimen 4. The median number of cycles per patient was 7 (range 2–18). Most treatment cycles (78 of 92; 85%) were administered as scheduled. Dose reduction was required for 10 cycles and most decreases were a result of toxicity (eight hematologic and no non-hematologic).

Efficacy

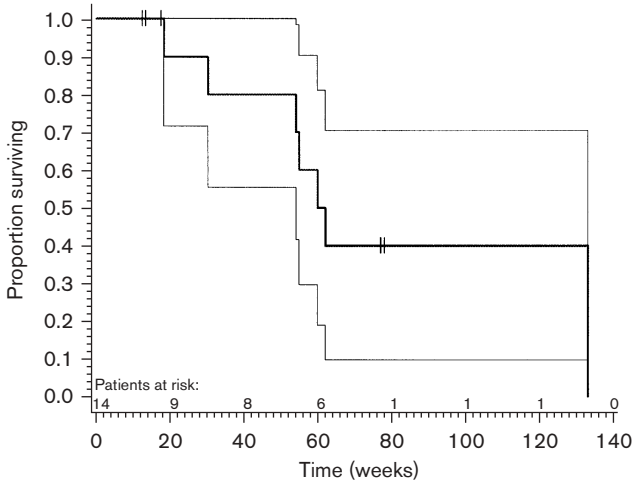
Of the 14 patients assessable for tumor response, one achieved a complete response and three achieved a partial response, giving an overall response rate of 28.6%. (Table 1). Eight patients showed stabilization of disease (57%) and two patients had progressive disease. The median progression-free survival was 28.5 weeks [95% confidence interval (CI) 13–62 weeks] (Fig. 1). No deaths occurred on treatment. The median overall

Table 1 **Demographic data of the patients enrolled in the study**

Number	Age	Sex	Therapy	Metastatic sites	Regimen	Cycles	Response	PFS	OAS
1	73	2	1	1,2	1	3	SD	25	30
2	72	1	1	1	2	18	CR	86	133
3	60	2	1	1	2	3	PD	12	18
4	63	1	1	1	2	12	SD	42	54
5	62	2	1	1,2,3,4,5	3	7	SD	32	55
6	63	2	1	1,5	4	8	PR	45	62
7	57	1	1	1	4	8	SD	62	77+
8	74	2	2	1	3	4	SD	21	60
9	77	1	1	1,2	3	2	PD	8	12+
10	72	1	1	1	3	4	SD	17	17+
11	63	2	1	1,5,6	3	8	PR	78	78+
12	57	1	1	1	3	8	SD	78	78+
13	65	2	1	1	3	4	PR	13	13+
14	57	2	1	1,6	3	3	SD	13	13+

Sex: 1=male, 2=female; *therapy*: 1=first-line therapy, 2=second-line therapy; *metastatic sites*: 1=liver, 2=lung, 3=skin, 4=lymph node, 5=bone marrow, 6=bone; *regimen*: 1=treosulfan 5 g/m^2 and gemcitabine 1 g/m^2 on day 1 every 21 days; 2=treosulfan 5 g/m^2 and gemcitabine 1 g/m^2 on day 1 every 28 days; 3=treosulfan 5 g/m^2 and gemcitabine 0.5 g/m^2 on day 1 every 21 days; 4=treosulfan 3.5 g/m^2 and gemcitabine 1 g/m^2 on day 1 and 8 every 21 days; *response:* CR=complete remission, PR=partial response, SD=stable disease, PD=progressive disease; *PFS*=progress-free survival; *OAS*=overall survival, both in weeks.

Fig. 2



Time of overall survival (weeks). The thick line represents the mean value of all patients, thin lines represent the 95% CI.

survival time was 61 weeks (95% CI 54–133 weeks) and the 1-year survival rate was 80% (95% CI 54–100%) (Fig. 2).

Tolerability and toxicity

All 14 patients were eligible for tolerability and toxicity assessments. The drug combination was generally well tolerated. All patients completed the scheduled 2 cycles of chemotherapy. Three patients were withdrawn because of toxicity (thrombocytopenia grade 4). As expected with these two drugs, neutropenia and thrombocytopenia were the most frequent adverse event (Table 2). Grade 4 neutropenia occurred in only one patient. Thrombocytopenia was noted in nine patients (64%), but was of grade 4 in only three patients (21.5%).

Table 2 **Hematologic and non-hematologic side-effects and toxicities**

Toxicity	Patients (% of 14 patients)
Mild hair loss	1 (7)
Neutropenia grade 2	1 (7)
Neutropenia grade 3	1 (7)
Neutropenia grade 4	1 (7)
Thrombopenia grade 2	0 (0)
Thrombopenia grade 3	2 (14)
Thrombopenia grade 4	3 (21.5)

All hematotoxicities were reported in patients treated according to regimens 3 and 4. No cases of hematologic toxicities were observed among treatment regimens 1 and 2. With the exception of mild hair loss in one patient, no other non-hematologic toxicities were seen.

Discussion

Metastatic uveal melanoma responds poorly to the currently available standard therapies. Several single-agent and combination chemotherapies originally established for the treatment of metastatic cutaneous melanoma showed very low antitumor activity in uveal melanoma and have produced response rates of less than 1%. The median survival for patients with initial liver metastases is only 7 months, with an estimated 1-year survival rate of 13% [2,15,16]. Thus, the search for more effective treatment options remains important in this field. Although previous clinical studies showed considerable chemoresistance, studies with chemoembolization of the liver using cisplatin- or fotemustine-based regimens have shown higher efficacy, yielding a response in 36–40% of patients [3,8,17]. The results of these studies suggest that at least some of these metastatic tumors are sensitive to chemotherapeutic agents. However, clinical trials with new drugs or drug combinations are difficult to perform since uveal melanoma is very rare with an incidence of about 0.6 to 0.7 cases per 100 000 [18].

Recent *ex vivo* results showed that a combination of treosulfan + gemcitabine effectively inhibited tumor growth of primary uveal melanoma cells in an ATP-based chemosensitivity assay and suggested that this combination might represent a promising regimen for untreated metastatic uveal melanoma patients. Although no clinical results have been reported, several institutions have already started open clinical studies of treosulfan + gemcitabine in metastatic uveal melanoma patients using schedules of this drug combinations that have been active in other types of cancer including breast and ovarian carcinoma [19]. The present study was designed to assess the efficacy and toxicity of this drug combination in uveal melanoma based on first clinical experiences in different European institutions treating this very rare tumor. To find out the most effective and well-tolerated scheme, patients were treated with four different regimens. The demonstration of one complete and three partial responses (28.5% response rate) in this study is particularly noteworthy. This objective response rate is higher than in most studies published worldwide. Furthermore, it is remarkable that nearly 60% of the patients showed disease stabilization in response to treosulfan + gemcitabine treatment. The regimen was well tolerated and adverse events were mild to moderate in the majority of patients. All hematologic toxicities were seen in patients treated with regimen 4 (treosulfan 3.5 g/m^2 and gemcitabine 1000 mg/m^2 on day 1 and 8 every 8 days). The reason for this effect is probably caused by the repetition of the therapy after 1 week. Furthermore, the efficacy of gemcitabine is mainly based on the inhibition of resistance mechanisms for treosulfan. Gemcitabine is transported into the cell using an ATP-dependent transport mechanism which is saturated in a concentration of 500 mg/m^2 and studies in pancreatic cancer could even prove that low doses of gemcitabine in combination with other chemotherapeutic drugs worked much better than high doses [20]. Increased gemcitabine doses therefore mainly seemed to produce more toxicities and additional bone marrow suppression without improvement of its intracellular accumulation. Finally, in further studies using a combination of gemcitabine and treosulfan, a maximum dose of gemcitabine of 500 mg/m^2 should not be exceeded. The median overall survival in this study group was 61 weeks (range 18–133 weeks), which is considerably higher compared to other therapeutic regimens tested [6,8]. In conclusion, these results suggest that treosulfan + gemcitabine may be more effective against uveal melanoma than other available chemotherapeutic drugs. The combination was generally well tolerated without any significant non-hematologic toxicity. The responses and overall survival rates achieved are encouraging, and provide a rationale for future clinical studies.

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